INTERVENTIONAL CARDIOLOGY

Implantation of paclitaxel-eluting stents in saphenous vein grafts: clinical and angiographic follow-up results from a multicentre study

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Objective: To define the clinical and angiographic follow-up results after implantation of paclitaxel-eluting stents (PESs) in stenotic saphenous vein grafts (SVGs).
Design: Prospective multicentre study. Comparison with a control group.
Methods: 60 consecutive patients with 65 lesions located in 65 SVGs (mean (SD) age of vein grafts 11.3 (5.7) years) treated with PES (V-Flex Plus, 2.7 µg/mm² paclitaxel, Cook) and 60 patients with 60 SVG lesions treated with bare metal stent (BMS) were included. Lesions had to be <20 mm in length and in grafts of 2.75–3.5 mm diameter. The 6 month angiographic follow-up was obtained on 51 lesions (79%) of the PES group and on 51 lesions (85%) of the BMS group.
Results: Baseline clinical and angiographic characteristics were comparable between both groups. At angiographic follow-up, three vein grafts in the PES group and five vein grafts in the BMS group were occluded. In-stent late lumen loss was lower in PES than in BMS (0.61 (0.81) vs 1.06 (0.72) mm, respectively; p = 0.021). In-stent binary restenosis rates were 12% vs 33%, respectively, (p = 0.012). Linear regression analysis showed BMS to be the only factor with an effect on late lumen loss (p = 0.011). Target-vessel failure rates were 18% in the PES group and 41% in the BMS group (p = 0.019), whereas major adverse cardiac event (MACE) rates at 180 days were 15% and 37%, respectively (p = 0.014).
Conclusions: Implantation of non-polymer-based PES in SVG lesions is associated with a lower late lumen loss and restenosis rate than those of BMS. There remains a substantial target-vessel failure rate and MACE rate even at 6 months owing to graft occlusion or new lesions in the graft.

D egenerative processes result in occlusion of 50% of saphenous vein grafts (SVGs) within 10 years.[1] Narrowing or occlusion of SVGs is associated with increased morbidity and mortality.[2] Implantation of bare metal stents (BMS) in SVGs has been associated with a considerable risk of restenosis and target-vessel failure.[3 4] Drug-eluting stents have considerably reduced the risk of restenosis when used in native vessels.[5–8] Only limited knowledge is available on the use of drug-eluting stents for treatment of SVGs. The mechanisms of in-stent restenosis in SVGs are similar to those in native vessels.[9] Thus, drug-eluting stents that reduce intimal hyperplasia should lower restenosis and also the need for target lesion revascularisation if used for treatment in SVGs.

This prospective multicentre study evaluated the efficacy of non-polymer-based paclitaxel-eluting stents (PES) for treatment of obstructed SVGs. These stents have been proved in the European evaLUation of pacliTaxel-Eluting Stent (ELUTES) Trial and the Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) to be effective in native coronary vessels.[8 10] Results were compared with those obtained with treatment of SVGs using BMS.

METHODS
Patients and lesions
This was a prospective multicentre study including three university-based study sites in Germany. A total of 60 consecutive patients with 65 de novo lesions located in 65 SVGs (mean (SD) age of vein grafts 11.3 (5.7) years) were treated with non-polymer-based PES (V-Flex Plus, coated directly with 2.7 µg/mm² paclitaxel, using a proprietary system of surface modification, Cook, West Lafayette, Indiana, USA). Lesions had to be <20 mm in length and in

SVGs of 2.75–3.5 mm diameter. A control group with implantation of bare metal stents was composed of 60 consecutive patients with 60 lesions in 60 SVGs (mean (SD) age of vein grafts 10.1 (4.5) years) treated at the University Aachen, Aachen, Germany, which fulfilled the same inclusion criteria with regard to lesion length and vessel diameter. These lesions were treated with BMS (34 lesions with Velocity Bx stents, Cordis (Warren, New Jersey, USA) and 36 lesions with Zeta stents, Guidant, Indianapolis, Indiana, USA) in the preceding period between 2002 and 2004 before the use of PES. The study was approved by the local ethical committees of the participating study centers.

Coronary intervention
Heparin was administered during the procedure according to standard practice. Aspirin (100 mg/day) and clopidogrel (300 mg loading dose) were started before the procedure. After the procedure, clopidogrel (75 mg/day) was administered for 6 months in addition to aspirin in the PES group and for 4 weeks in the BMS group. In case of predilatation, a stent length longer than the initial balloon length was encouraged. Stents were available in lengths of 12, 16, 20, 24 and 28 mm and in diameters of 2.5, 3 and 3.5 mm in both groups. Stent placement with the use of a distal protection device was recommended and performed in 34 cases of the PES group and in 28 cases of the control group. In the 28 patients of the PES

Abbreviations: ASPECT, Asian Paclitaxel-Eluting Stent Clinical Trial; BMS, bare metal stent; ELUTES, European evaLUation of pacliTaxel-eluting stent; MACE, major adverse cardiac events; MLD, minimal lumen diameter; PES, paclitaxel-eluting stent; SVG, saphenous vein graft; TIMI, thrombolysis in myocardial infarction; TLR, target lesion revascularisation

Table 1 Baseline clinical characteristics

	Non-polymer based PES (n = 60)	BMS (n = 60)	p Value
Mean (SD) age (years)	67 (11)	67 (7)	0.996
Men, n (%)	54 (90)	56 (93)	0.746
Prior myocardial infarction, n (%)	30 (50)	27 (45)	0.717
Diabetes mellitus, n (%)	15 (25)	17 (28)	0.845
Arterial hypertension, n (%)	52 (87)	46 (77)	0.244
Hyperlipidaemia, n (%)	53 (88)	52 (87)	1
Unstable angina, n (%)	28 (47)	31 (52)	0.864
Mean (SD) number of CABG	3.3 (0.9)	3.4 (0.7)	0.511
Mean (SD) age of CABG (years)	11.3 (5.7)	10.1 (4.5)	0.266

BMS, bare metal stent; CABG, coronary artery bypass graft; PES, paclitaxel-eluting stent.
Arterial hypertension: arterial pressure >160/90 mm Hg or medically treated.
Hyperlipidaemia: serum cholesterol >240 mg/l or medically treated.

group presenting with unstable angina, 18 (64%) were treated with distal protection devices, and, in the 31 patients of the BMS group, 16 (52%) were treated with distal protection devices.

In-hospital and 6-month clinical follow-up
Procedural success was defined as <30% final diameter stenosis in the treated lesion and the absence of major clinical complications (in-hospital death, Q-wave myocardial infarction or emergency coronary bypass surgery). All patients were monitored for 6 months after the procedure for any major adverse cardiac event (MACE): defined as death, myocardial infarction, stent thrombosis, need for target lesion revascularisation (TLR) or target-vessel revascularisation, either percutaneous or surgical. Target-vessel failure was defined as need for recurrent target-vessel revascularisation, restenosis >50% or complete vessel occlusion.

Baseline clinical demographics, in-hospital complications and the occurrence of death, myocardial infarction and late recurrent coronary intervention during follow-up were verified by independent hospital chart review and source documentation.

Quantitative coronary angiography
Quantitative angiographic analysis was performed at the angiographic core laboratory of the University Aachen using a validated quantitative angiographic system (CAAS II System, PieMedical, Maastricht, The Netherlands) with the contrast-filled catheter as the calibration standard. Quantitative measurements included reference diameter, lesion length, minimal lumen diameter (MLD) in lesion (defined as the in-stent segment plus proximal and distal 5 mm edge segments) and in-stent (without adjacent edge segment) before and after the procedure and at follow-up. Late lumen loss (defined as the reduction in minimum lumen diameter from immediately after the procedure to the 6-month follow-up), acute gain (defined as the increase in minimal luminal diameter immediately after percutaneous transluminal coronary angioplasty), net gain (the difference between the acute gain and late lumen loss) and loss index (the ratio of late lumen loss to acute gain) were calculated. The lesion was described as ostial when it was within 3 mm of the coronary ostia.

Statistical analysis
Statistical analysis was performed with the use of the SPSS software. Categorial data were presented as frequencies and compared with Pearson's χ^2 test. Continuous data were presented as mean (SD) and compared with the Student's t

test or analysis of variance as adequate. The primary end point of this study was to show an advantage for the PES group compared with the BMS group with regard to the late lumen loss. The sample size was calculated on the basis of an expected late loss of 1 (0.8) mm for the BMS group and of 0.5 (0.7) mm for the PES group with a type I error of 5% and a type II error of 20%, resulting in a sample size of 36 lesions with requested angiographic follow-up. Multivariate analysis to identify predictors for angiographic restenosis was performed, including diabetes mellitus, reference vessel diameter, lesion length, MLD in lesion before intervention and the stent being a PES or a BMS, as parameters. A p value <0.05 was considered significant.

RESULTS
Baseline characteristics
Clinical characteristics at baseline were similar between the two groups (table 1).

Procedural characteristics
Stent placement was possible in all lesions of the BMS group and in 64 lesions (98%) of the PES group. Stent length, diameter and implantation pressure were similar between the two groups (table 2).

There were four vessels with thrombolysis in myocardial infarction (TIMI)2 flow after stent placement in the PES group and two vessels with TIMI2 flow after stent placement in the BMS group. All other vessels had TIMI3 flow after the procedure.

Angiographic results
Baseline angiographic results were similar for the two groups. The 6-month follow-up angiography was performed on 51 lesions (79%) of the PES group and on 51 lesions (85%) of the BMS group (table 3).

Three stents in the PES group and five stents in the BMS group were occluded at follow-up. Patients in the PES group showed a larger in-stent and in-lesion MLD at 6 months than those in the BMS group. Figure 1 illustrates the cumulative frequency distribution curves for the in-stent MLD before and after stent implantation and at follow-up. A significantly lower in-stent late lumen loss was observed with PES than with BMS (0.61 (0.81) vs 1.06 (0.72) mm, respectively; p = 0.021). This also translated into a significantly lower binary in-stent restenosis rate in the polymer-based PES group than in the BMS group (table 3).

Owing to three new lesions distant from the initial lesion site in addition to restenosis, target vessel failure at 6 months was

Table 2 Baseline lesion and procedural characteristics

	Non-polymer based PES (n = 65)	BMS (n = 60)	p Value
Location of lesion, n (%)			0.767
Ostial	12 (18)	13 (22)	
Proximal	20 (31)	14 (23)	
Mid	18 (28)	16 (27)	
Distal and anastomotic	15 (23)	17 (28)	
Distal protection devices, n (%)	34 (52)	28 (47)	0.656
No reflow	0	0	1
Mean (SD) number of stents per lesion	1.13 (0.33)	1.08 (0.28)	0.441
Mean (SD) length of stent (mm)	16.7 (3.7)	14.6 (4.4)	0.078
Mean (SD) maximal balloon diameter (mm)	3.3 (0.3)	3.4 (0.6)	0.728
Mean (SD) maximal implantation pressure (atm)	12 (2)	11 (3)	0.524

BMS, bare metal stent; PES, paclitaxel-eluting stent.

Table 3 Quantitative angiographic results

	Non-polymer based PES (number of lesions = 51)	BMS (number of lesions = 51)	p Value
Preintervention			
Lesion length (mm)	11.8 (4.1)	10.8 (3.8)	0.231
Reference lumen diameter (mm)	3.05 (0.52)	3.06 (0.60)	0.775
Minimal lumen diameter (mm)	0.91 (0.4)	1.07 (0.52)	0.012
Diameter stenosis (%)	70 (12)	63 (11)	0.007
Postintervention			
Minimal lumen diameter in stent (mm)	2.89 (0.40)	2.8 (0.46)	0.309
Minimal lumen diameter in lesion (mm)	2.85 (0.41)	2.77 (0.45)	0.312
Diameter stenosis in stent (%)	6 (10)	9 (8)	0.956
Diameter stenosis in lesion (%)	6 (10)	9 (8)	0.934
Follow-up			
Reference lumen diameter (mm)	3.01 (0.51)	2.96 (0.45)	0.386
Minimal lumen diameter in stent (mm)	2.28 (0.72)	1.71 (0.62)	0.001
Minimal lumen diameter in lesion (mm)	2.22 (0.72)	1.7 (0.65)	0.001
Diameter stenosis in stent (%)	25 (24)	42 (26)	0.003
Diameter stenosis in lesion (%)	26 (24)	43 (27)	0.003
Late loss in stent (mm)	0.61 (0.81)	1.06 (0.72)	0.021
Late loss in lesion (mm)	0.63 (0.79)	1.05 (0.75)	0.023
Loss index in stent (mm)	0.34 (0.44)	0.66 (0.62)	0.002
Binary restenosis in stent, n (%)	6 (12)	17 (33)	0.012

BMS, bare metal stent; PES, paclitaxel-eluting stents.
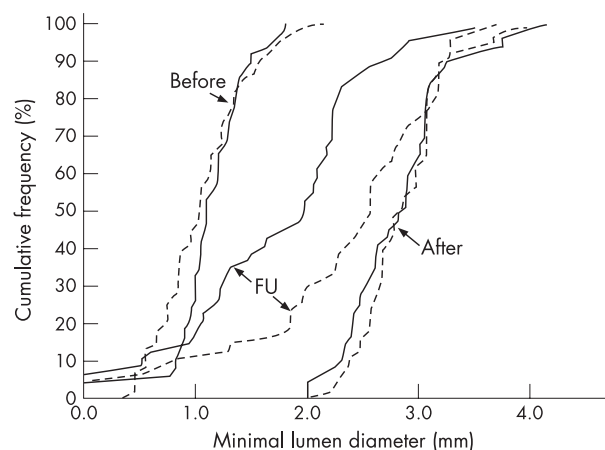Values are mean (SD) unless otherwise specified.

Figure 1 Cumulative frequency distribution curves for in-stent minimal lumen diameter for both study groups before stent placement, after stent placement and at follow-up (FU). The dotted lines relate to the non-polymer-based paclitaxel-eluting stent group and the solid lines relate to the bare metal stent group.

seen in 9 (18%) vessels of the PES group and in 21 (41%) vessels of the BMS group (p = 0.019).

Predictors of binary restenosis

In a multivariate model, independent predictors of binary restenosis were the type of stent being a BMS (odds ratio (OR) = 5.21, 95% confidence interval (CI) 1.22 to 22.2; p = 0.027), and the minimal lumen diameter before stent placement (OR = 0.17, 95% CI 0.04 to 0.76; p = 0.02). In a linear regression analysis, stent being a BMS was found to be the only parameter with an effect on late lumen loss (p = 0.011).

Clinical follow-up results

At the 30-day follow-up, a MACE rate of 0% was observed in both study groups. No cases of stent thrombosis were noted during the 6-month follow-up period.

At the 6-month follow-up, TLR was performed in 4 (6%) lesions of the PES group and in 13 (22%) lesions of the BMS group (p = 0.024). MACE at 6 months was observed in 9 of the 60 (15%) patients with PES. In the BMS group, the MACE rate was higher at 37% (22 of 60) patients (p = 0.014) (fig 2).

DISCUSSION

Use of drug-eluting stents in SVGs has not been extensively evaluated so far. This study shows[1] improved angiographic and clinical follow-up results after treatment of stenotic SVGs with PES as compared with treatment using BMS,[2] still a substantial rate of target-vessel failure and MACE after treatment of stenotic SVGs using PES owing to new lesions in the SVG.

Treatment of stenotic SVGs

Interventional treatment of obstructive vein graft disease is associated with a high risk of procedural and follow-up

treatment failures. The increased peri-procedural risks in these patients is related to the nature of degenerated vein graft lesions with potential distal atheroembolisation resulting in microvascular obstruction. The high risk of follow-up treatment failure in SVGs compared with native coronary vessels is related to an increased risk of restenosis at the target site and progression of disease at other sites of the vein grafts causing target vessel failure. The risk of distal embolisation has been markedly reduced with the use of distal protection devices.[11 12] The risk of restenosis could be reduced with the use of BMS as compared with the use of balloon angioplasty and has become the default interventional modality in SVGs.[3 4] However, even with the use of BMSs, at least 30–40% of SVGs fail over the next 12–18 months owing to restenosis in half of the cases and progression of subclinical atherosclerotic disease elsewhere than the original stented lesion in the other half.[3] In this study, late lumen loss and restenosis rate in the BMS group were comparable to these results. In an attempt to reduce distal embolisation and restenosis, composite stent grafts with polytetrafluoroethylene membrane have been used.[13 14] However, on the basis of available data from the STents In GraftsTrial and Randomized Evaluation of polytetrafluoroethylene COVERed stent in saphenous vein grafts trial, stent grafts do not deliver any benefit over BMS with regard to follow-up results. The mechanism of in-stent restenosis in vein grafts is also neointimal hyperplasia and the response of in-stent restenosis to brachytherapy is as effective as that to native vessels.[9 15] Thus, the benefit from antiproliferative drug-eluting stents should be similar to that seen in native vessels. Data on the use of drug-eluting stents in vein grafts are limited to non-randomised studies with control groups having different baseline characteristics.[16–19] Ge et al[16] reported on the use of sirolimus-eluting stents in 35 patients and PES in 26 patients for treatment of vein graft lesions. The restenosis rate was shown to be 10% for this combined drug-eluting stent group, which was markedly lower than for a control group treated in the preceding time period with BMSs. This result was seen despite a considerably larger reference vessel and stent diameters in the BMS group than in the drug-eluting stent group. In addition, the MACE free survival rate was higher in the drug-eluting stent group than in the control group.

Paclitaxel has been shown to suppress vascular cell proliferation and subsequent excessive formation of intimal hyperplasia.[7 8] Randomised clinical trials on the use of polymer-based
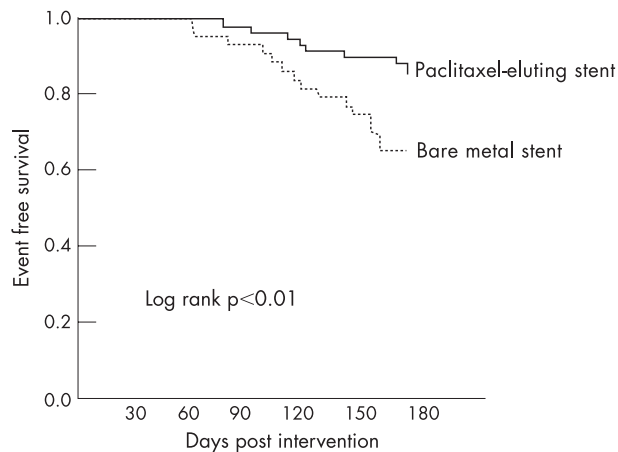
Figure 2 Kaplan–Meier survival curves for freedom from major adverse cardiac events.

PES in native coronary lesions have shown remarkable and consistent effectiveness of polymer-based PES in the reduction of in-stent restenosis and repeat TLR.[7] Non-polymer-based drug delivery has been suggested as a different approach to deliver paclitaxel, which circumvents the potential limitations of a polymer coating such as local hypersensitivity to the polymer with subsequent excessive inflammation. The multicentre ASPECT ELUTES, and DELIVER I (the RX Achieve drug-eluting coronary stent system in the treatment of patients with de novo native coronary lesions) evaluated PES without polymer coating for treatment of de novo native coronary lesions.[8 10 20] A significant reduction of neointimal hyperplasia and restenosis were observed in the high-dose groups of the ASPECT and ELUTES Trials.

Treatment using paclitaxel-eluting stents in this study

This study showed a significant advantage of using non-polymer-based PES in the treatment of obstructed vein grafts compared with BMS with regard to late lumen loss, restenosis rate and clinical events. Thus, the study supports the use of drug-eluting stents for obstructed SVG. Recent data have indicated that sirolimus-eluting stents may be more effective to lower late lumen loss and restenosis than polymer-based PES. Furthermore, on the basis of data from the DELIVER I and II Trials, the effectiveness of the non-polymer-based PES to reduce restenosis seems less reliable than for polymer-based PES. Thus, further studies will be required to define whether stents with sirolimus coating may be even more effective to suppress restenosis and recurrent target lesion revascularisation in SVGs than shown in this study.

Study limitations

This was not a randomised study. Patients were enrolled to the two study groups in a sequential manner. However, to our knowledge this is the first multicentre study with equal clinical and angiographic baseline characteristics, which used only one drug-eluting stent type and involved a high angiographic follow-up rate. The study inclusion criteria requested vein graft diameters of ⩽3.5 mm. This was because of the non-availability of the evaluated PES in diameters >3.5 mm. Thus, large vein graft diameters were excluded from this study. From studies on native vessels, it is known that the risk of restenosis reduces with increasing size of the vessel.[21 22] Thus, the advantage of drug-eluting stents may be smaller in vein grafts of greater diameter.

CONCLUSION

Implantation of non-polymer-based paclitaxel-eluting stents in new SVG lesions is associated with a lower late loss, restenosis rate and target lesion revascularisation rate than those of BMS. However, there remains a substantial target-vessel failure rate and MACE rate even at 6 months owing to graft occlusion or new lesions in the graft.

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